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Predictors, symptom dynamics and neural mechanisms of bipolar disorders

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CHAPTER 6

Association Between the Fronto-Limbic Network and Cognitive and Emotional Functioning in Individuals With Bipolar Disorder
A Systematic Review and Meta-analysis

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Abstract

Patients with bipolar disorder (BD) suffer from cognitive and emotional dysfunctions. Various brain circuits are implicated in BD but have not been investigated in a meta-analysis of functional Magnetic Resonance Imaging (fMRI) studies. The aim of the current fMRI meta-analysis is to investigate the brain functioning of BD patients compared with healthy controls (HC) in three domains: emotion processing, reward processing, and working memory.

Data were abstracted from articles found through a systematic literature search. The literature search included all the fMRI studies on BD before March 2020. Only fMRI original research studies comparing adult BD patients with HC were included. Studies had to include a task assessing at least one of the domains. i.e., emotion processing, reward processing, or working memory. Differences in brain region activity were tested with whole-brain analysis using the activation likelihood estimation method.

In accordance with PRISMA guidelines, a total of 49 fMRI studies (999 BD, 1027 HC) were included after the selection procedure: 20 studies used an emotion processing task (316 BD, 369 HC), nine studies used a reward processing task (215 BD, 213 HC), and 20 studies used a working memory task (530 BD, 417 HC). As compared to healthy subjects, BD patients showed hyperactivation in the amygdala and hippocampus and hypoactivation in the inferior frontal gyrus during emotion processing, hyperactivation in the orbitofrontal cortex during reward processing, and hyperactivation in the ventromedial prefrontal cortex and subgenual anterior cingulate cortex during working memory activity. Limbic hyperactivation was only found during euthymia in emotion and reward processing domains; abnormalities in frontal cortex activity were also found in BD patients with mania and depression.

This meta-analysis revealed evidence for activity disturbances in key brain areas involved in cognitive and emotion processing in BD patients. Most of the regions are part of the fronto-limbic network. The results suggest that aberrations in the fronto-limbic network, present in both euthymic and symptomatic patients, may be underlying cognitive and emotional dysfunctions in BD.

6.1 Introduction

Bipolar disorder (BD) is a severe psychiatric disorder and is characterized by recurrent depressive and (hypo)manic episodes[1]. These mood fluctuations contribute significantly to functional impairments, including dysfunction in education and work[2]. In addition to affective symptoms, patients with BD show cognitive impairments and emotion regulation deficits during episodes and also during euthymia[3, 4, 5]. As a result, several of these deficits in BD may be considered as a trait-related characteristic of BD. Abnormalities in a variety of brain regions and related circuitry could be underlying cognitive and emotion regulation deficits in BD, with studies in general describing predominantly aberrations in the fronto-limbic network[6, 7, 8, 9], a group of interconnected neural regions including the prefrontal cortex (PFC), amygdala, anterior cingulate cortex (ACC), hippocampus, and nucleus accumbens[10].

BD patients appear to show amygdala hyperactivation during emotion processing across multiple tasks that evoke emotional responses[11]. In addition, recent work shows reduced functional connectivity between the ventrolateral PFC (vlPFC), ACC, orbitofrontal cortex (OFC), and limbic areas, which points towards a more complex aberrant interplay between frontal and limbic structures, instead of amygdala hyperactivity alone[10]. In addition to emotion, BD patients show increased activity in fronto-limbic regions during reward processing, amongst others in the PFC, ACC, and striatum[12, 13, 14]. Studies of working memory in BD have reported deviant frontal cortex activity[15, 16, 17], including medial frontal gyri hyperactivation[18] and dorsolateral PFC (dlPFC) hypoactivation[19, 20, 21].

Across all emotional and cognitive domains, inconsistent findings have been found, and as a result a robust hypothesis on fronto-limbic dysfunction in BD is lacking[22]. Not surprisingly, and probably related to aberrant brain activity, BD patients showed behavioral deficiencies in terms of decreased task performance during emotion and reward processing, as well as during cognitive tasks that demand working memory activity[4, 23, 24, 25, 26]. In addition to decreased task performances, fronto-limbic network deficiencies may also be involved in aberrant psychological mechanisms in BD such as state-independent emotional hyper-reactivity, rumination and the intense pursuit of goals and focus on achievement[27, 28, 29].

Cognitive and emotion tasks that involve fronto-limbic brain activity have been intensively studied. Emotion processing involves attentional processes towards (emotional) stimuli, their interpretation, and the regulation of activated emotions (the ability to monitor and modify the occurrence, intensity, and duration of an ongoing response to emotional stimuli)[30]. Activations in subcortical regions are strongly associated with modulating and generating emotions, whereas frontal regions are involved in the evolution and regulation of emotional responses[10, 26]. The three primary functions of reward processing include associative learning (classical conditioning and operant reinforcement), incentive salience (motivation and desire), and positively-valenced emotions (pleasure and hedonic)[31]. In particular, pleasure coding reward has been described to be associated with activation in the OFC[32], whereas ACC activity is related to reward anticipation[33]. In addition to the ACC, the ventral striatum has a key function in anticipation of reward stimuli and is part of a complex circuit involving limbic regions such as the amygdala, attributing feelings towards the experienced reward[34]. Working memory is seen as a platform where

information temporarily can be held, manipulated, and then used to adjust goal-directed behavior[35, 36]. Studies of working memory have pointed to the involvement of the dlPFC, dorsal and anterior ACC, and parietal cortex[37]. The dlPFC is associated with the integration and retrieval of information that is stored or taxing load[38]. The ACC is implicated in evaluative processes to adjust and adapt the received information depending on demand[39]. In addition to fronto-limbic regions, the parietal cortex seems to be a workspace for processing sensory and perceptual information[40, 41, 42]. In sum, tasks associated with emotion processing, reward processing, and working memory are all dependent on an adequate activation of fronto-limbic brain regions and can therefore be used to assess functioning in this network.

Although there is an increasing number of fMRI studies suggesting fronto-limbic functional abnormalities in BD, a meta-analysis specifically focusing on this brain network in BD has not yet been performed. A meta-analysis of fronto-limbic network activity in BD is important as malfunctioning of this brain network can be considered as reflecting part of the pathophysiology of cognitive and emotional impairments in BD. Therefore, in the current study, we conducted a meta-analysis of fMRI studies in patients with BD investigating emotion processing, reward processing, or working memory, domains which all rely on proper fronto-limbic network activity. By performing this meta-analysis, we aim to aggregate the evidence to be able to draw more rigorous conclusions regarding the potential abnormalities in the fronto-limbic network in BD. Moreover, we want to elucidate if trait (i.e., euthymia) or state (i.e., mania or depression) affects potential fronto-limbic network alterations.

6.2 Methods

6.2.1 Literature search and selection

For the selection procedure PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[43, 44] guidelines were followed (see eTable 6.3 in Appendix). The PRISMA flow chart depicting the process for the systematic literature search and selection of the studies is shown in eFigure 6.4 (Appendix). The literature search was conducted in the databases of PubMed, Embase, Web of Science, COCHRANE Library, PsycINFO, Emcare, Academic Search Premier, and ScienceDirect. The following keywords were used in the literature search: bipolar disorder, manic depression, functional magnetic resonance imaging (fMRI), mania, and bipolar depression (see appendix for the extensive literature search). Articles were eligible if written in English and with subjects between 18 and 65 years old. All healthy controls (HC) were physically and neurologically healthy, with no current psychopathology. Exclusion criteria for all participants were medical or neurological illnesses that might influence brain function, and any contraindications for receiving an MRI scan. Literature reviews, meta-analyses, methodological articles, case reports, letters, conference abstracts, and editorials were excluded. Selection of literature was conducted using three main inclusion criteria: 1) task-related fMRI studies on BD with whole-brain analyses, 2) studies had to include a task assessing at least one of the domains. i.e. emotion processing, reward processing, or working memory, 3) studies compared adult patients with BD with HC. Exclusion criteria were: fMRI studies using a region-of-interest (ROI) analysis approach, only assessing functional connectivity, and resting-state studies. Additionally, studies including only subjects with high-risk for BD, BD relatives, BD offspring, or childhood BD (<18 years) were excluded. Finally, the studies were grouped into at least one of the three domains.

For each study, data were extracted (i.e. first author, year of publication, mean age, gender, number of BD patients and HC, mood state, contrasts, details about tasks, imaging results as coordinated clusters [X,Y,Z] in voxels and details of the fMRI paradigm), which were used for description and further analyses. The fMRI studies were allocated to three task domains (i.e., emotion processing, reward processing, and working memory). Two fMRI studies examined two different domains and were therefore included in two different analyses[13, 45].

6.2.2 Statistical analysis

Meta-analyses were conducted using the software GingerALE version 3.0.2[43, 44]. Differences in brain activation among regions associated with each domain were analyzed separately using the activation likelihood estimation (ALE) method. The ALE approach uses modeling of activation locations (foci) by a 3D Gaussian, calculating the overlap of the distributions across experiments using the spatial uncertainty of the foci[44]. It forms a probabilistic map of the likelihood that each voxel was activated by an experiment.

The analyses for each domain involved two analyses of contrasts. First, we analyzed the activation in brain areas that were more active in BD brains compared to HC, indicating hyperactivation in BD. Second, we analyzed the activation in brain areas which were more

active in HC brains compared to BD, referring to hypoactivation in BD. The voxel-level Family-Wise Error (FWE) method ($p = 0.05$) was used for the correction of all the analyses and contrasts of different domains. The number of threshold permutations was set at 1000, and the p-value threshold at 0.05 with a minimum cluster size of suprathreshold voxels exceeding 100 mm^3. Next, we performed sensitivity analyses focused on mood states. For each domain, we analyzed the effect of mood states separately (euthymic, manic, and depressive). For these analyses, a similar procedure was followed.

6.3 Results

In total, 49 whole-brain-based fMRI studies were included, which accrued 999 BD patients and 1027 HC. The included studies (per domain) and their clinical specifications are listed in eTable 6.3 (Appendix). All meta-analytical results are presented in Table 6.1 and 6.2.

6.3.1 Emotion processing

For emotion processing, a total of 20 studies were included, with in total 324 patients with BD and 369 HC. Patients with BD had different mood states; 116 (35.8%) were euthymic, 70 (21.4%), depressed, 44 (13.6%) were (hypo)manic, one mixed state (0.3%), and the rest were not specified (n = 93, 28,7%). The emotion processing domain included emotion tasks with a variety of paradigms including emotionally salient stimuli (i.e., affect induction, emotional perception of facial emotions or prosody, emotion regulation, emotion recognition, emotion memory, or inhibition tasks.

Hyperactivation was shown in all BD patients compared with HC (Table 6.1) in a part of the left hippocampus, the left and right anterior temporal cortex, and the left amygdala (Figure 6.1A). Hypoactivation in BD patients was found only in the right inferior frontal gyrus (IFG) as compared to HC (Figure 6.1B).

The results regarding mood states (Table 6.2) revealed hyperactivation in the left parahippocampal gyrus and hypoactivation in the left IFG in BD patients who were in the euthymic state. During mania, we found hyperactivation in the left thalamus and hypoactivation in right IFG in patients with BD.

6.3.2 Reward processing

A total of nine studies on reward processing were included, with in total 195 BD patients and 213 HC. 117 (60%) of BD patients were euthymic, 65 (33.3%) depressed, 10 (5.1%) were (hypo)manic and three were in a mixed state (1.5%). The reward processing domain paradigms included monetary incentive, gambling, card number guessing, and Roulette tasks.
Taking all BD patients together (Table 6.1), only hyperactivation in the left OFC was shown as compared to HC (Figure 6.2).

For euthymic mood state in BD patients, hyperactivation was found in the left parahippocampal gyrus, ACC, MFG, and right temporal gyrus compared to HC. Patients who were in a depressive mood state showed hyperactivation in the left IFG and in the right superior temporal gyrus (see Table 6.2). A meta-analysis in manic BD patients could not be performed due to a lack of power.

6.3.3 Working memory

We included 20 studies with 530 BD patients and 417 HC for working memory. There were 178 (36.1%) patients in euthymic state, 171 (34.7%) depressed patients, 124 (25.1%)

(hypo)manic, and 57 (10.8%) were not specified. The majority of the studies used a letter n-back task and a few studies a delayed match to sample task.

Overall, hyperactivation in BD patients was found in the subgenual ACC (sgACC) and ventromedial PFC (vmPFC) (Figure 6.3) as compared to HC (Table 6.1).

With regard to mood states, no difference in euthymic BD patients were found compared to HC. Patients who were (hypo)manic showed hyperactivity in left ACC and hypoactivation in left IFG during working memory. Depressed BD patients showed hyperactivation in the left PFC and ACC; hypoactivation was found in the right partial lobe and left cerebellum (see Table 6.2).

Anatomical label	Peak coordinates x	y	z	BA	Z	Cluster size (mm^3)	ALE Value
Emotion processing							
Bipolar disorder → Healthy controls							
left Hippocampus	-18	-14	-10	28	6.70	864	0.0293
right Superior temporal gyrus	48	14	-10	38	6.06	176	0.0251
left Superior temporal gyrus	-56	-16	6	41	5.86	176	0.0251
left Amygdala	-28	-2	-12	-	5.52	160	0.0217
Healthy controls → Bipolar disorder							
right Inferior frontal gyrus	42	22	0	47	6.38	232	0.0241
Reward processing							
Bipolar disorder → Healthy controls							
left Orbitofrontal cortex	-46	30	0	47	6.22	344	0.0240
Working memory							
Bipolar disorder → Healthy controls							
left Subgenual anterior cingulate	-6	34	-10	32	6.82	696	0.0323
left Ventromedial prefrontal cortex	-2	46	-10	10	6.63	624	0.0308

Table 6.1: Activation likelihood estimation meta-analytical results of whole brain-based studies. Talairach coordinates are reported. BA = Brodmann area. The voxel-level Family-Wise Error (FWE) method (p = 0.05) was used for the correction of all the analyses and contrasts of different domains. The number of threshold permutations was set at 1000, and the p-value threshold at 0.05 with a minimum cluster size of suprathreshold voxels exceeding 100 mm 3.

Table 6.2: Activation likelihood estimation meta-analytical results of whole brain-based studies per mood state. Talairach coordinates are reported. BA = Brodmann area. The voxel-level Family-Wise Error (FWE) method (p = 0.05) was used for the correction of all the analyses and contrasts of different domains. The number of threshold permutations was set at 1000, and the p-value threshold at 0.05 with a minimum cluster size of suprathreshold voxels exceeding 100 mm 3.

N.S. = Not Significant, N.A. = Not Applicable due to limited power.

	Peak coordinates						
Anatomical label	x	y	z	BA	Z	Cluster size (mm^3)	ALE Value
Emotion processing							
Euthymia							
Bipolar disorder → Healthy controls							
left Parahippocampal gyrus	-24	-20	-10	28	5.62	216	0.0191
Healthy controls → Bipolar disorder							
left Inferior frontal gyrus	-56	10	26	9	5.28	168	0.0141
Mania							
Bipolar disorder → Healthy controls							
left Thalamus	-4	-32	10	-	5.91	312	0.0176
Healthy controls → Bipolar disorder							
right Inferior frontal gyrus	46	26	-2	47	5.31	224	0.0141
Depression							
Bipolar disorder → Healthy controls							
left Angular gyrus (Parietal Lobe)	-32	-56	32	39	5.63	104	0.0183
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.S.
Reward processing							
Euthymia							
Bipolar disorder → Healthy controls							
left Parahippocampal gyrus	-22	-42	-10	36	5.81	152	0.0188
left Anterior cingulate	-16	42	0	32	5.81	152	0.0188
left Medial frontal gyrus	-16	48	-6	10	5.81	152	0.0188
right Middle temporal gyrus	60	-4	-8	21	5.81	152	0.0188
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.A.

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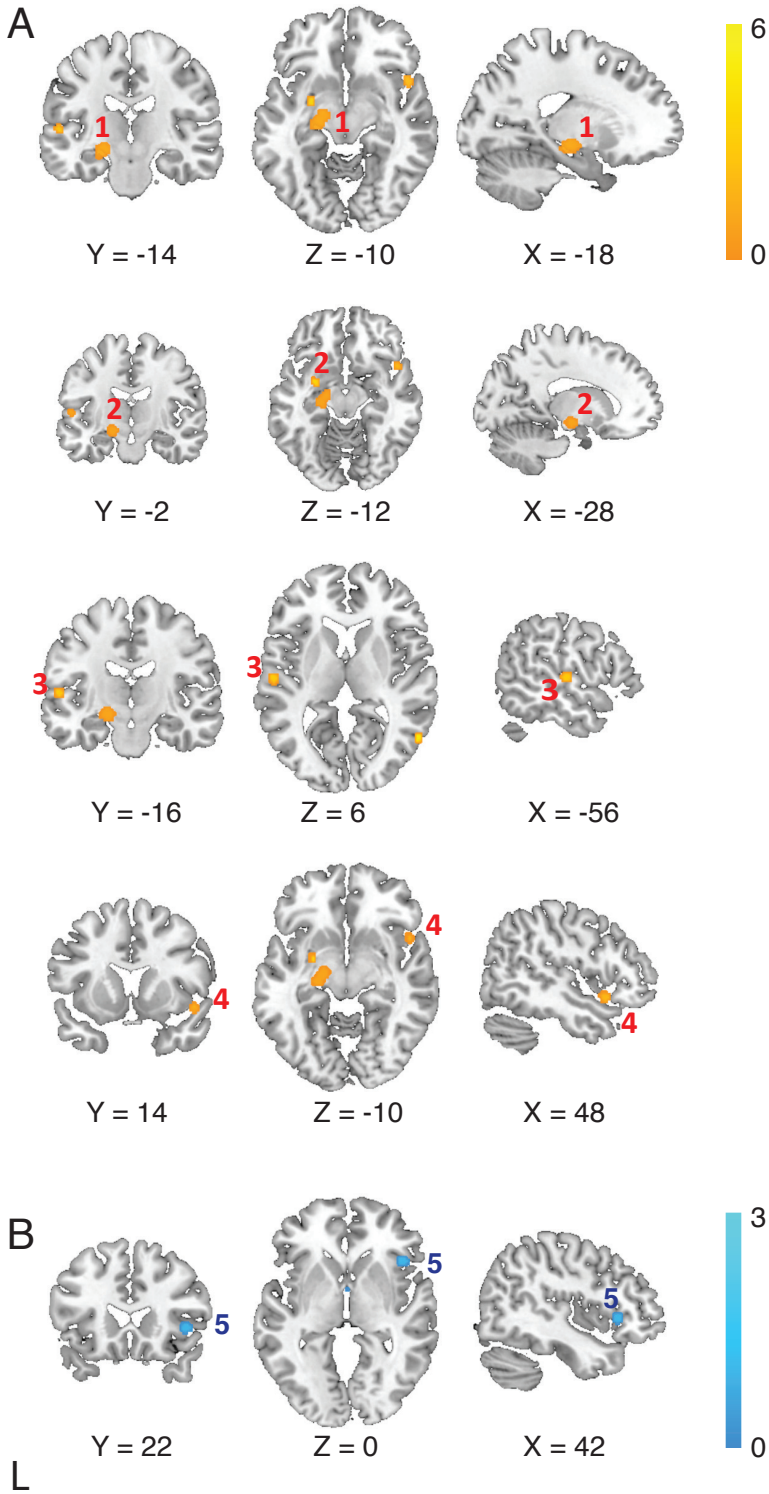
Table 6.2 – continued from previous page

Anatomical label	Peak coordinates x	y	z	BA	Z	Cluster size (mm^3)	ALE Value
Depression							
Bipolar disorder → Healthy controls							
left Inferior frontal gyrus	-48	28	-1	47	5.46	100	0.0170
right Superior temporal gyrus	48	-22	-2	22	5.65	100	0.0175
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.S.
Mania							
Bipolar disorder → Healthy controls	-	-	-	-	-	-	N.A.
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.A.
Working memory							
Euthymia							
Bipolar disorder → Healthy controls	-	-	-	-	-	-	N.S.
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.S.
Mania							
Bipolar disorder → Healthy controls							
left Anterior cingulate	-6	40	4	32	6.26	400	0.0224
Healthy controls → Bipolar disorder							
left Middle frontal gyrus	-30	-6	56	6	8.30	624	0.0367
Depression							
Bipolar disorder → Healthy controls							
left Prefrontal cortex	-2	46	-10	10	7.18	504	0.0277
left Anterior cingulate	-4	36	-4	32	5.76	112	0.0189
Healthy controls → Bipolar disorder							
right Parietal lobe	8	-66	56	7	5.70	112	0.0184
left Cerebellum	-30	-52	-32	-	5.71	104	0.0185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Y = -14
Z = -10
X = -18
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Y = -2
Z = -12
X = -28
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3
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Y = -16
Z = 6
X = -56
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4
Y = 14
Z = -10
X = 48
B
5
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Y = 22
Z = 0
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Figure 6.1: Meta-analytic maps of brain functional changes of domain emotional processing : significant brain hyperactivation (A) in 1. left hippocampus, 2. left amygdala, 3. left anterior temporal cortex and 4. right anterior temporal cortex. Significant brain hypoactivation (B) in 5. right IFG. The right side of all coronal and axial images corresponds to the right side of the brain. Colorbars represent z-values.

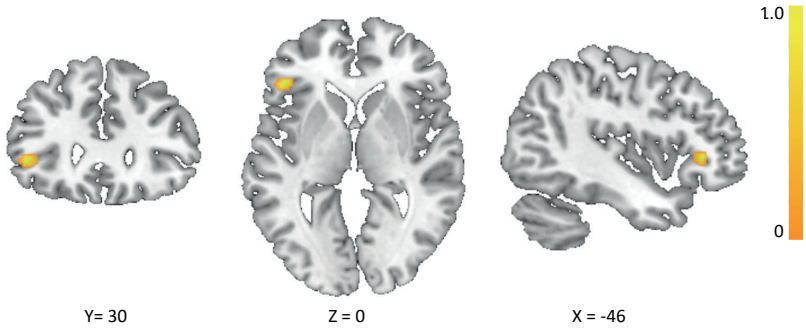

Figure 6.2: Meta-analytic maps of brain functional changes of domain reward processing: significant brain hyperactivation in left OFC. The right side of all coronal and axial images corresponds to the right side of the brain. Colorbar represents z-values.

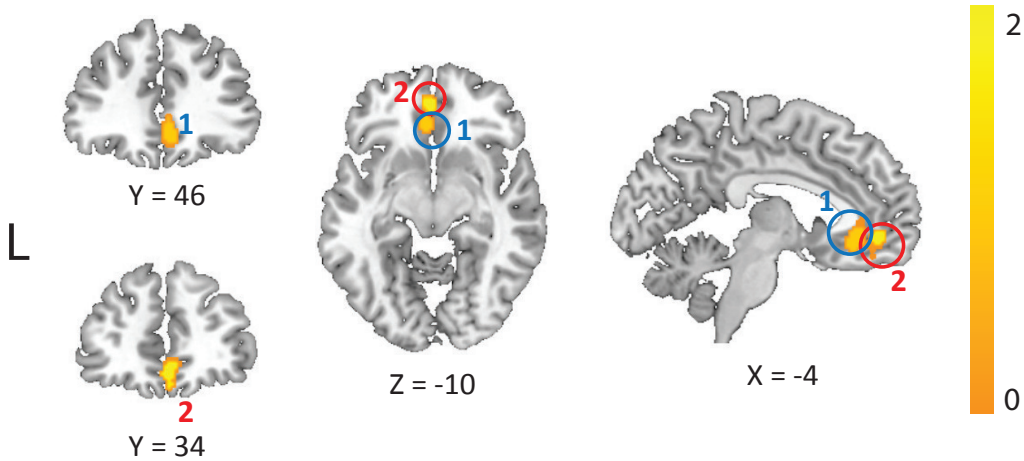

Figure 6.3: Meta-analytic maps of brain functional changes of domain working memory : significant brain hyperactivation in left 1. subgenual anterior cingulate and 2. ventromedial PFC. The right side of all coronal and axial images corresponds to the right side of the brain. Colorbar represents z-values.

6.4 Discussion

In the current meta-analysis, we investigated brain functioning in patients with BD as compared to HC within cognitive domains related to emotion processing, working memory, and reward processing. Our findings revealed significant differences in brain activity in BD patients mostly within the fronto-limbic network. Specifically, limbic activation alterations were only manifested in euthymic BD patients, whereas more widespread frontal dysfunctions were also found during depression and mania. As such, one can assume that aberrant limbic activity during cognitive and emotion processing may be a trait-related BD characteristic, on the other hand, disruptions in frontal cortex activity may be associated with state-related factors.

During emotion processing, we found that patients with BD showed hyperactivation in the hippocampus, parts of the temporal cortex, and amygdala, and hypoactivation in the right IFG (as part of the PFC) when all affective states are pooled together. This is in line with an earlier meta-analysis[7] and a systematic review[11] that focused on emotion processing and found abnormal activity in the fronto-limbic network. Our results regarding the emotion processing domain can be functionally interpreted. For instance, amygdala hyperactivation may be interpreted as reflecting a state of 'oversensitivity', resulting in increased amygdala responses even when there is no need to. The amygdala has a crucial role in emotion generation (i.e. perception and arousal), identification of emotional stimuli[46, 47, 48], and emotion regulation[49]. In addition to amygdala hyperactivation during emotion processing, we also found increased activation in the hippocampus. Besides its crucial role in memory, this region is also involved in socio-emotional processing and the production of affective states[48, 50]. Further, hyperactivation was found in the temporal cortex, which is notably involved in social and emotion processing, recognition, and semantic memory[51]. Our results regarding emotion processing also encompassed hypoactivation in the IFG, which is known to be associated with inhibitory control[52]. Inhibition is a major subcomponent of executive function and is defined as the ability to suppress the process of irrelevant stimuli and dominant response when inappropriate[53]. The inability to inhibit responses is, among others, associated with impulsive behavior[54]. Moreover, BD patients might have difficulties in the identification of emotional stimuli (either negative or positive) leading to increased arousal, making it more difficult to regulate their emotions and this, in turn, may provoke mood episodes states[55]. From a network perspective, hypoactivity in inhibitory structures such as the IFG might be related to hyperactivity in the whole network related to fronto-limbic system (as found here; hippocampus, parts of the temporal cortex, and amygdala) that normally should be inhibited[56].

For reward processing, our results showed hyperactivation in the left OFC in BD. OFC activity is important for pleasure coding as well as reward outcome and for processing the experience of hyperhedonia[32]. This region forms the key in a hypersensitivity model of reward processing that was introduced based on a behavioral approach system (BAS) hypothesis for BD[57]. The concept of BAS refers to the hypothesis that bipolar patients have a hypersensitive reward system that leads to overreaction or underreaction to reward-related cues. It states that excessive reward system activation leads to (hypo)manic symptoms, whereas excessive deactivation gives rise to depressive symptoms[57]. This model is thought to be associated with hyperdopaminergia which leads to high-risk, high-reward

seeking behavior observed during mania[58]. Our finding of OFC hyperactivation in BD is in line with this reward hypersensitivity model of BD.

To our best knowledge, no previous meta-analyses of neuroimaging studies have focused on the reward system in bipolar patients. To date, only a systematic review on imaging findings during reward processing in unaffected first-degree relatives has been performed[59]. Although relatives are non-affected and do not have symptoms, these genetically at-risk subjects seem to show reward-related activity dysfunction similar to BD patients, i.e. increased OFC in response to reward[59]. The fact that the current meta-analysis in a large sample of BD patients found a similar OFC activity pattern as found in healthy relatives, underlines the importance of these aberrations as they may serve as an important element in the pathological pathway towards BD.

For working memory tasks, our results showed hyperactivation in the sgACC and vmPFC as compared to HC. Interestingly, these regions are connected to limbic structures and are functionally involved in reward valuation and emotion regulation, but recent studies highlight the role in working memory as well. Both sgACC and vmPFC play an important role in integrating cognitive and emotional stimuli. For example, the vmPFC structurally connects the amygdala with the dlPFC and functionally regulates the influencing effects of capacity-exceeding working memory load from the dlPFC and the mediating deleterious effects of emotional interference on cognitive processing in the amygdala[60, 61]. In addition, the sgACC is seen as another bridge between the dlPFC and amygdala, and plays a role in emotional processing and attention[62]. The interconnection of these two regions to the dlPFC and the amygdala facilitates interactions between emotion and cognition[61]. Our results provide further support for the potential role of dysregulated vmPFC and sgACC activity as a direct contributor to poor working memory performance and deficiencies in emotional processing in BD.

In addition to the whole BD group, analyses were also performed per mood state. Limbic hyperactivity was only found in euthymic BD patients (parahippocampal), whereas abnormalities in frontal activation, although with a more widespread pattern, were also revealed during states of depression and mania. A tentative conclusion can be drawn that limbic hyperactivation during emotion and cognitive processing in BD may be a trait-dependant characteristic, whereas frontal cortex dysfunction may also be affected during states in BD. Functionally, failed frontal inhibitory control may be more pronounced when patients suffer from a depressive or manic episode, while the earlier mentioned increased limbic 'oversensitivity' may only occur during euthymia and may potentially be a risk factor for provoking mood states[55]. Given power constraints, these conclusions should be interpreted with caution. It can therefore not be ruled out that increased limbic activity could also be the case during mania or depression, however, the current meta-analysis shows that frontal hypoactivation may be a more robust state-dependent finding. One could hypothesize that during affective states BD patients take high-dose or other medication as compared to euthymia, which may potentially normalize limbic activity[63].

Two earlier meta-analyses with smaller numbers of inclusions investigated task fMRI studies in BD[7, 64]. Our findings regarding emotional processing are consistent with limbic hyperactivation and IFG hypoactivation as found in one meta-analysis[7]. However, all kinds of paradigms related to a variety of cognitive functions were included, while the

current meta-analysis focused on working memory, emotional and reward processing with regard to the hypothesis of impaired fronto-limbic network activity in BD specifically. One other meta-analysis focused on the comparison between BD youth and adults[64]. Interestingly, similar amygdala hyperactivation during emotional tasks and pgACC hyperactivation during non-emotional tasks was found in BD youth, which underlines the important role of these brain areas in the psychopathology of BD and suggest common trait-like abnormalities.

To the best of our knowledge, this is the first meta-analysis showing robust fronto-limbic network abnormalities during emotion and cognitive functioning. The differentiation of three cognitive domains in relation to fronto-limbic network functioning in BD allowed a better perspective on how neurocognitive abnormalities can co-exist in parallel.

Some limitations need to be noted. First, although significant results were revealed in the analyses per mood state, the number of BD subjects for the different states was limited. As mentioned above, this may result in the negative finding of unincreased limbic activity during affective states. Future studies specifically focusing on state-related emotional and cognitive functioning are required to increase the power of meta-analyses. Second, we were unable to perform sensitivity analyses and disentangle the potential effects of psychopharmaceuticals due to heterogeneity in medication[65]. The great majority of patients was treated with a mood-stabilizer as monotherapy or in combination with other psychotropics. However, a review in BD patients found no significant medication effects on brain activation[66]. Third, clinical heterogeneity and demographic features often make it complicated to compare across studies. To obtain generalizable results, we included a broad range of studies, conditions, and multiple contrasts in three domains of interest, although cognitively impaired subjects were excluded. Meta-analytic results help one to draw overriding conclusions and identify consistency in the literature despite heterogeneity, while they might lack specificity as to the nature of any aberration. A final limitation is that we could not correct for specific participant factors, including symptomatology such as psychosis. A few studies measured and reported psychotic symptoms, while others did not mention anything. In addition, because of the lack of information, we also did not model gender, medication and comorbidity, factors that might have effects on brain activity in patients with BD. However, it is known that in particular mood states are strongly associated with confounding fMRI results, specifically the fronto-limbic network[67]. In the current analyses, we were able to tackle this important factor.

The current study is the first meta-analysis in BD patients investigating brain activity during cognitive and emotional tasks that demand proper fronto-limbic functioning. We were able to demonstrate that the fronto-limibic network is thoroughly affected in BD, both in euthymic as well as symptomatic patients. Regarding reward processing specifically, more studies are needed to replicate and expand our findings. Moreover, fMRI studies in BD would benefit from the standardization of reward paradigms. Finally, the field will be furthered by using novel approaches such as multimodal analyses and pattern-recognition techniques. These advances will likely increase the clinical and scientific relevance of reward processing fMRI paradigms in BD, which may result in their use during diagnostics or in investigating therapeutic targets. Longitudinal fMRI studies following at-risk patients as well as first-onset BD patients are needed to examine the development of cognitive impairments and its association with fronto-limbic findings over the course of BD.

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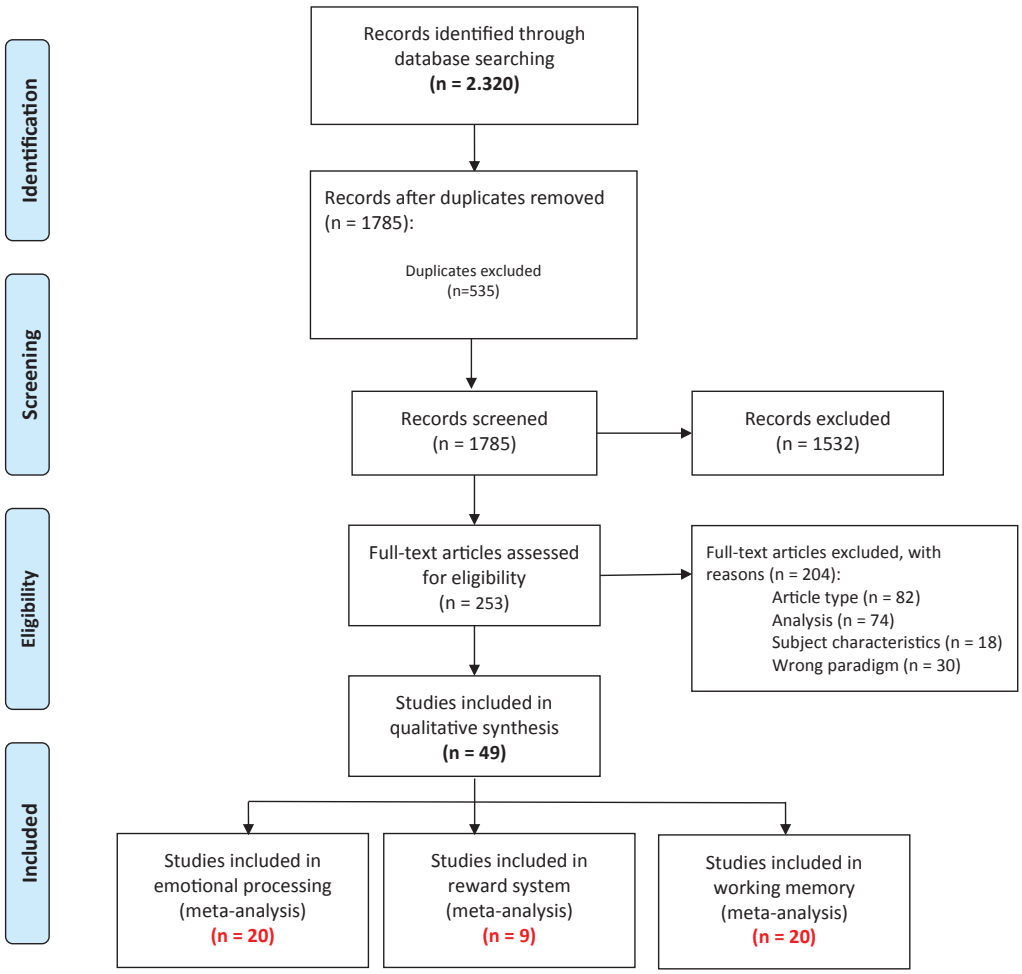
6.5 Supplementary Online Content

eMethods. Literature search
The literature search included all the fMRI studies on BD before March 2020. An independent employee of the Walaeus Library (Leiden University Libraries) performed the literature search. The auteurs screened first for eligibility based on titles and abstracts according to the inclusion and exclusion criteria. When this was unclear, the full-text review was carried out. The full-text of the remaining studies was beside the auteurs reviewed independently by two interns in the field of psychology. Disagreements were managed by discussion to reach a consensus.

We used the following key words (using both free-text and MeSH search):

(("fMRI"[tw] OR "f mri"[tw] OR fmr imag∗[tw] OR functional magnetic∗[tw] OR "functional magnetic resonance imaging"[tw] OR "functional mri"[tw] OR "functional mr"[tw] OR ("Magnetic Resonance Imaging"[mesh] AND "functional"[tw]) OR (("Magnetic Resonance Imaging"[mesh] OR MR imag∗[tw] OR "MRI"[tw] OR "magnetic resonance"[tw]) AND ("Functional Neuroimaging"[Mesh:noexp] OR functional imag∗[tw] OR functional neuroimag∗[tw]))) AND ("Bipolar Disorder"[Mesh] OR "Bipolar and Related Disorders"[Mesh] OR "Bipolar Disorder"[tw] OR "Bipolar Disorders"[tw] OR "Manic-Depressive Psychosis"[tw] OR "Manic Depressive Psychosis"[tw] OR "Bipolar Affective Psychosis"[tw] OR "Manic-Depressive Psychoses"[tw] OR "Mania"[tw] OR "Manias"[tw] OR "Manic State"[tw] OR "Manic States"[tw] OR "Bipolar Depression"[tw] OR "Manic Disorder"[tw] OR "Manic Disorders"[tw] OR "manic depressive"[tw] OR "manic"[tw] OR Bipolar affectiv∗[tw] OR Bipolar disease∗[tw] OR Bipolar disorder∗[tw] OR bipolar depress∗[tw]) NOT ("Animals"[mesh] NOT "Humans"[mesh])

Figure 6.4: PRISMA Flow chart.
PRISMA flow chart of the literature search for included studies.



	BD patients	BD type	HC	BD patients	HC	Mood states	Medication	Task
	female n (%)	I/II (n)	female n (%)	mean age (SD)	mean age (SD)	(n)	Mood Stabilizers (n) Antipsychotics (n) Antidepressants (n)	
Emotion Tasks								
(Cerullo et al. 2014)[1]	25 (68%)	I (25)	25 (67%)	30.0 (8.0)	26.0 (7.0)	Depressed (25)	Unmedicated (25)	Modified continuous performance task emotional and neutral distracters (CPT-END)
(Mitchell et al. 2004)[2]	11 (0%)	NS (11)	13 (0%)	42.8 (1.8)	32,2 (3.6)	Not specified (11)	MS (9), AP (4), AD (5)	Emotional prosody task
(Wessa et al. 2007)[3]	17 (41%)	I (10), II (7)	17 (35%)	44.9 (12.7)	44.9 (13.4)	Euthymic (17)	MS (7), AP (8)	Affective go/no-go task
(Whalley et al. 2009)[4]	14 (29%)	I (14)	14 (26%)	35.4 (8.4)	38.4 (10.0)	Not specified (14)	MS (4), AP (8), AD (3)	Emotional memory task
(Young, Bodurka, and Drevets 2016)[5]	16 (88%)	I (16)	16 (88%)	37.6 (9.3)	37.8 (8.7)	Depressed (16)	Unmedicated (16)	Emotional autobiographical memory task
(Morris et al. 2012)[6]	13 (38%)	I (13)	15 (60%)	41.0 (3.0)	35.0 (2.0)	Euthymic (6); Hypomanic (5); Not specified (2)	AP (5), AD (6)	Emotion regulation task
(Zhang et al. 2020)[7]	15 (33%)	I (13), II (2)	15 (60%)	39.9 (12.5)	33.6 (11.1)	Depressed (2); Not specified (13)	AP (15), AD (9)	Emotion regulation task
(Han et al. 2018)[8]	10 (40%)	I (10)	10 (40%)	38.6 (9.4)	31.8 (8.0)	Euthymic (10)	MS (10), AD (8)	Emotional picture task
(Moser et al. 2018)[9]	37 (32%)	I (37)	48 (42%)	27.5 (8.1)	29.8 (8.5)	Not specified (27)	MS (15), AP (30), AD (7)	Emotion recognition task
(Kryza-Lacombe et al. 2019)[10]	33 (78%)	I (21), II (11)	22 (55%)	38.2 (11.1)	29.4 (7.2)	Depressed (8); Hypomanic (4); Mixed (1); Euthymic (44)	MS (29), AP (18), AD (15)	Face emotion labelling task
(Elliott et al. 2004)[11]	8 (50%)	I (7), II (1)	11 (73%)	35.0 (-)	37.6 (9.7)	Manic (8)	MS (7), AP (5)	Affective go/no-go task
(Foland et al. 2008)[12]	9 (66%)	I (9)	9 (66%)	34.6 (8.0)	30.4 (7.6)	Manic (9)	MS (8), AP (1)	Face emotion labelling task
(Lennox et al. 2004)[13]	10 (20%)	I (10)	12 (50%)	37.3 (12.8)	32.6 (10.7)	Manic (10)	MS (10), AP (8)	Face emotion labelling task
(Malhi et al. 2007)[14]	10 (100%)	I (10)	10 (100%)	33.5 (8.7)	33.6 (6.4)	Euthymic (10)	MS (7)	Explicit facial emotion recognition task
(Altshuler et al. 2008)[15]	11 (54%)	I (11)	17 (47%)	32.0 (7.3)	29.5 (6.6)	Depressed (11)	MS (8), AP (2), AD (3)	Face-matching task
(Chen et al. 2006)[16]	16 (19%)	I (16)	8 (75%)	Manic = 39 (13.4) Depressed = 41.9 (12.1)	38.75 (12.5)	Manic (8); Depressed (8)	MS (16), AP (6), AD (2)	Explicit and implicit face recognition task
(Jogia et al. 2008)[17]	12 (58%)	I (12)	12 (58%)	42.1 (11.8)	41.8 (10.9)	Not specified (12)	MS (12)	Sad affect face recognition task
(Hassel et al. 2008)[18]	19 (52%)	I (19)	24 (54%)	32.5 (8.8)	27.7 (8.7)	Euthymic (19)	MS (12), AP (14), AD (9)	Facial expression task
(Killgore, Gruber, and Yurgelun-Todd 2008)[19]	14 (21%)	NS (14)	13 (8%)	28.1 (11.2)	25.5 (4.7)	Not specified (14)	MS (5), AP (12), AD (1)	Fearful face perception task
(Lagopoulos and Malhi 2007)[20]	10 (100%)	I (10)	10 (100%)	33.6 (8.12)	33.6 (6.7)	Euthymic (10)	MS (7)	Emotional Stroop task

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Table 6.3 – continued from previous page

	BD patients	BD type	HC	BD patients	HC	Mood states	Medication	Task
	female n (%)	I/II (n)	female n (%)	mean age (SD)	mean age (SD)	(n)	Mood Stabilizers (n) Antipsychotics (n) Antidepressants (n)	
Reward Tasks								
(Abler et al. 2008)[21]	12 (42%)	I (12)	12 (42%)	33.9 (11.2)	36.2 (11.2)	Manic (8); Mixed (3); Hypomanic (1)	MS (12)	Monetary incentive task
Caseras et al. 2013)[22]	32 (59%)	I (17), II (15)	20 (65%)	42.3 (6.0)	41.6 (7.7)	Hypomanic (1); Euthymic (31)	MS (22), AP (12), AD (12)	Monetary reward processing task
(Chase et al. 2013)[23]	23 (82%)	I (23)	37 (67%)	33.9 (8.5)	33.1 (6.2)	Depressed (25)	MS (13), AP (11), AD (9)	Card number guessing task
(Frangou et al. 2008)[24]	7 (71%)	I (7)	7 (71%)	37.0 (5.9)	39.0 (5.9)	Euthymic (7)	MS (7)	Gambling task
(Jogia et al. 2012)[25]	36 (53%)	I (36)	37 (43%)	42.5 (10.6)	37.6 (11.3)	Euthymic (36)	Unmedicated (14), A (21), AP (6), AD (7)	Iowa gambling task
(Kirschner et al. 2019)[26]	25 (36%)	I (25)	25 (36%)	37.3 (9.1)	33.1 (9.7)	Euthymic (25)	MS (18), AP (18), AD (7)	Monetary incentive delayed task
(Manelis et al. 2019)[27]	34 (85%)	I (34)	17 (59%)	35.1 (1.3)	31.4 (1.5)	Depressed (16); Euthymic (18)	MS (10), AP (19), AD (15)	Card number guessing task
(Mason et al. 2014)[28]	20 (50%)	I (18), II (2)	20 (55%)	36.0 (4.3)	33.25 (9.3)	Euthymic (20)	MS (8)	Roulette task
(Sharma et al. 2016)[29]	24 (58%)		30 (55%)	38.0 (11.7)	39.4 (11.8)	Depressed (24)	MS (11), AP (11), AD (6)	Monetary reward procedure
Working Memory Tasks								
(Adler et al. 2004)[30]	15, unknown	I (15)	15, unknown	29.0 (9.0)	30.0 (9.0)	Euthymic (15)	Unmedicated (4) Unknown (11)	Letter n-back task
(Brooks et al. 2015)[31]	19 (42%)	II (19)	19 (52%)	36.7 (11.4)	42.6 (12.0)	Depressed (19)	Unmedicated (19)	Letter n-back task
(Deckersbach et al. 2008)[32]	9 (100%)	I (9)	17 (100%)	27.6 (2.8)	25.6 (5.9)	Depressed (9)	MS (9)	Letter n-back task (with mood induction)
(Drapier et al. 2008)[33]	20 (45%)	I (20)	20 (50%)	42.7 (10.4)	41.9 (11.6)	Euthymic (20)	MS (16), AP (4), AD (2)	Letter n-back tasks
(Fernández-Corcuera et al. 2013)[34]	41 (45%)	NS (41)	41 (41%)	40.4 (10.2)	40.3 (9.8)	Depressed (41)	Unmedicated (41)	Letter n-back task
(Frangou et al. 2008)[24]	7 (71%)	I (7)	7 (71%)	37.0 (5.9)	39.0 (5.9)	Euthymic (7)	MS (7)	Letter n-back task
(Gruber et al. 2010)[35]	18 (44%)	I (18)	18 (61%)	38.2 (9.9)	33.9 (11.5)	Euthymic (18)	Unmedicated (3) MS (12), AP (3), AD (6)	Verbal delayed-match-to-sample task
(Hamilton et al. 2009)[36]	21 (38%)	I (21)	38 (39%)	36.4 (10.7)	32.5 (11.7)	Euthymic (21)		Delayed match to sample task
(Jogia et al. 2012)[25]	36 (53%)	I (36)	37 (43%)	42.5 (10.6)	37.6 (11.3)	Euthymic (36)	Unmedicated (14) MS (21), AP (6), AD (7)	Letter n-back task
(Lagopoulos, Ivanovski, and Malhi 2007)[37]	10 (100%)	I (10)	10 (100%)	32.4 (10.8)	31.7 (11.9)	Euthymic (10)	MS (7)	Delay-response memory task
(McKenna et al. 2014)[38]	23 (65%)	I (23)	23 (65%)	45.3 (9.5)	44.8 (10.6)	Euthymic (23)	MS (17), AP (12), AD (11)	Pseudoword delayed match to sample task
(Monks et al. 2004)[39]	12 (100%)	I (12)	12 (100%)	45.8 (3.5)	45.6 (3.5)	Euthymic (12)	MS (12)	Letter n-back task Sternberg task

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Table 6.3 – continued from previous page

	BD patients	BD type	HC	BD patients	HC	Mood states	Medication	Task
	female n (%)	I/II (n)	female n (%)	mean age (SD)	mean age (SD)	(n)	Mood Stabilizers (n) Antipsychotics (n) Antidepressants (n)	
(Pomarol-Clotet et al. 2012)[40]	29 (37%)	I (29)	46 (41%)	49.8 (12.1)	36.3 (13.6)	Manic (n = 29)	MS (23), AP (24)	Letter n-back task
(Pomarol-Clotet et al. 2015)[41]	114 (54%)	I (108), II (6)	38 (52%)	39.9 (10.2)	39.7 (8.9)	Manic (38); Depressed (38); Euthymic (38)	MS (95), AP (69), AD (32)	Letter n-back task
(Robinson et al. 2009)[42]	15 (53%)	I (15)	15 (47%)	39.0 (12.6)	36.2 (10.6)	Euthymic (15)	MS (8), AP (7), AD (12)	Delayed-non-match-to-sample task
(Wu et al. 2014)[43]	20 (52%)	I (20)	29 (50%)	27.9 (6.4)	22.7 (5.1)	Not specified (n =20)	MS (18), AP (7), AD (12)	Letter n-back task
(Rodríguez-Cano et al. 2017)[44]	26 (61%)	I (26)	26 (61%)	45.6 (9.2)	46.8 (11.2)	Depressed (26)	MS (23), AP (14), AD (15)	Letter n-back task
(Moser et al. 2018)[9]	37 (32%)	I (37)	48 (42%)	27.5 (8.1)	29.8 (8.5)	Not specified (37)	MS (15), AP (30), AD (7)	Various stimuli n-back task
(Goikolea et al. 2019)[45]	31 (48%)	I (31)	31 (48%)	30.5 (9.1)	31.1 (8.8)	Manic (31)	MS (22), AP (31)	Letter n-back task
(Alonso-Lana et al. 2019)[46]	26 (42%)	I (26)	26 (42%)	39.2 (12.3)	40.2 (11.0)	Manic (baseline) (26); Euthymic (follow-up) (26)	MS (19), AP (22), AD (2)	Letter n-back task

Table 6.3: Descriptives of included fMRI studies of three domains of emotion processing, reward processing and working memory in the meta-analysis using a whole-brain approach. A total of 46 papers has been used including 49 fMRI studies.
NS = Not Specified, MS = Mood Stabilizers, AP = Antipsychotics, AD = Antidepressants.